PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: George L. Murphy et al.	Group Art Unit: 1637
Serial No.: 09/613,535	Examiner: Spiegler, A.H.
Filed: July 10, 2000	Atty. Dkt. No.: AMBI:055US
For: METHODS FOR RECOMBINATORIAL NUCLEIC ACID SYNTHESIS	

CERTIFICATE OF MAILING
37 C.F.R 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-01450, on the date below:

February 10, 2005
Date

Mark B. Wilson

DECLARATION OF GEORGE L. MURPHY, ROBERT A. SETTERQUIST, AND ANDREW D. ELLINGTON UNDER 37 C.F.R. § 1.131

We, George L. Murphy, Robert A. Setterquist, and Andrew D. Ellington, hereby declare as follows:

1. We are the inventors of the subject matter of all claims currently pending in the referenced patent application.

2. We understand that the Patent and Trademark Examiner found the claimed subject matter of the referenced application to be anticipated by U.S. Patent Application Serial No. 2001/0044111.

3. We are submitting this Declaration to set forth evidence that we invented the subject matter of the claimed invention prior to March 20, 2000, the priority date of U.S. Patent Application Serial No. 2001/0044111.

4. All of the work described in this declaration was performed in the United States.

5. As evidence of our conception, we attach, as Exhibit 1, pages describing all technological aspects of the invention from an invention disclosure made following Ambion, Inc. standard procedures prior to March 20, 2000.

6. The attached invention disclosure describes, for example, annealing a defined primer nucleic acid to a first single stranded nucleic acid and performing a first extension wherein a dideoxynucleotide is incorporated into the extension product (see Step 5). Step 6 describes removing the dideoxynucleotide from the extended nucleic acid. Step 7 describes denaturing the extended nucleic acid from the first template nucleic acid, annealing the extended nucleic acid to a second template nucleic acid whose sequence is not identical to the first template nucleic acid, and performing a second extension wherein a dideoxynucleotide is incorporated into the twice extended nucleic acid. Step 7 also provides that Steps 6 and 7 can be repeated a desired number of times.

7. We were diligent in reducing the claimed invention to practice from the time of the invention disclosure up to and including the July 10, 2000 filing date of the instant patent application.

8. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date: _____ _____
George L. Murphy

Date: _____ _____
Robert A. Setterquist

Date: 2/2/05 Andrew D. Ellington
Andrew D. Ellington

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In re Application of: George L. Murphy et al.	Group Art Unit: 1637
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February 2, 2005
Date

Mark R. Wilson

DECLARATION OF GEORGE L. MURPHY, ROBERT A. SETTERQUIST, AND ANDREW D. ELLINGTON UNDER 37 C.F.R. § 1.131

We, George L. Murphy, Robert A. Setterquist, and Andrew D. Ellington, hereby declare as follows:

1. We are the inventors of the subject matter of all claims currently pending in the referenced patent application.

2. We understand that the Patent and Trademark Examiner found the claimed subject matter of the referenced application to be anticipated by U.S. Patent Application Serial No. 2001/0044111.

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Date: _____ _____
George L. Murphy

Date: _____ _____
Robert A. Setterquist

Date: _____ _____
Andrew D. Ellington

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Date: _____

George L. Murphy

Date: 02-01-05

Robert A. Setterquist

Date: _____

Andrew D. Ellington

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Date: 1/29/05

George L. Murphy

Date: _____

Robert A. Setterquist

Date: _____

Andrew D. Ellington

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February 2, 2005
Date

Mark B. Wilson

DECLARATION OF ROBERT A. SETTERQUIST, Ph.D. UNDER 37 C.F.R. § 1.132

I, Robert A. Setterquist, Ph.D., hereby declare as follows:

1. I am a U.S. citizen residing at 3704 Lost Oasis Hollow, Austin, TX 78739. I am Senior Scientist at Ambion, Inc. I have extensive experience in the field of molecular biology. References containing examples of my work are included in my *Curriculum vitae*. A copy of my *Curriculum vitae* is attached as Exhibit 1.

2. I have reviewed the Office Action dated November 2, 2004, the specification of the present application, the pending claims, the amendments to the claims, and Short *et al.* (WO 98/01581).

3. I understand that the Examiner considers that the term "defined primers" does not distinguish the method of the claimed invention from the method disclosed in Short *et al.* (WO 98/01581) ("Short"). Based on my experience as a molecular biologist, I do not find this to be the case.

4. Based on the teachings of the present specification, a molecular biologist would understand that the term "defined primer" as used in the claimed method is a primer that generates extension products that share a defined 5' end. Moreover, the current claims further clarify that the extended nucleic acids have essentially identical 5' ends. This is described in the specification at page 38, line 21 to page 39, line 7, and FIG. 1.

5. In particular, the specification states that "all or virtually all fragments will have 5' sequences defined by an initiating oligonucleotide." Specification, p. 38, ln. 24-25. The specification further states that in preferred methods, a pool of fragments are generated having "defined 5' ends and staggered, terminated ends, such that the lengths of the members preferably differ by a single nucleotide (FIG. 1)." Specification, p. 38, ln. 28-30. A review of FIG. 1 and the description of FIG. 1 on page 16 of the specification illustrate the use of a "defined primer" as recited in the presently claimed methods.

6. The present specification defines a "chain terminating agent" as an agent that terminates chain elongation upon incorporation into an elongated chain, see page 34, lines 24-27. The Action notes that Short recites "chain terminators" in claims 1-3 on pages 67-68, and thus the Action asserts that Short teaches dideoxynucleotides and dideoxynucleotide analogs. Although a molecular biologist would understand the term "chain terminator" to include dideoxynucleotides and dideoxynucleotide analogs, a molecular biologist would not understand Short's use of the term "chain terminator" to include dideoxynucleotides and dideoxynucleotide analogs for the following reasons. First, Short does not mention dideoxynucleotides or dideoxynucleotide analogs. Second, the mode of termination described by Short is different from the presently claimed method of using dideoxynucleotides or dideoxynucleotide analogs as chain terminating agents that are incorporated into the extending nucleic acid sequence. Moreover, Short's method recited in claims 1-3 would

not appear to work with an agent that terminates chain elongation upon incorporation into an elongating chain, because subjecting the resultant polynucleotides to a second amplification would not be possible if the first amplification had been terminated with a dideoxynucleotide or dideoxynucleotide analog unless the polynucleotides' 3' OH was first restored. Short does not appear to teach this essential step.

7. The Action also alleges that the DNA adducts function similarly to dideoxynucleotides. I do not find this to be the case based on my experience in the field of molecular biology. A molecular biologist would understand a DNA adduct to be an agent that binds to a nucleic acid. A DNA adduct does not block the synthesis of the nascent strand by being incorporated into the nascent strand. Rather, a DNA adduct functions to block extension of the nascent strand by binding to the template strand.

8. The Action also alleges that the 5-bromouracil functions similarly to a dideoxynucleotide. I do not find this to be the case based on my experience in the field of molecular biology. The incorporation of 5-bromouracil into an elongating nucleotide sequence does not terminate elongation. In contrast, the incorporation of a dideoxynucleotide into an elongating nucleotide sequence terminates elongation. A molecular biologist, therefore, would understand that 5-bromouracil and a dideoxynucleotide do not function similarly to terminate chain elongation.

9. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date: 2-2-05

Robert A. Setterquist